FINAL REPORT

CRUDE MCHM

HAEL No.: 97-0216 **EAN: 972790**
PM No.: 18717-00

ACUTE ORAL TOXICITY STUDY IN THE RAT

GUIDELINE

OECD: 401
EEC: Annex V., Test B.1

AUTHOR

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TESTING FACILITY

Toxicological Sciences Laboratory
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USA

LABORATORY PROJECT ID

97-0216A8

STUDY SPONSOR

Eastman Chemical Company
P.O. Box 431
Kingsport, TN 37662-5280

STUDY COMPLETION DATE

December 1, 1999

QUALITY ASSURANCE INSPECTION STATEMENT
(21 CFR 58.35(B)(7), 40 CFR 792.35(B)(7), AND 40 CFR 160.35(B)(7))

STUDY: 97-0216-1 STUDY DIRECTOR: BERNARD,L.G. PAGE 1
11/10/99

ACCESSION NUMBER: 972790

STUDY TYPE: ACUTE ORAL TOXICITY

M. L James 11/10/99
(AUDITOR, QUALITY ASSURANCE UNIT) DATE

THIS STUDY WAS INSPECTED BY 1 OR MORE PERSONS OF THE QUALITY ASSURANCE UNIT. WRITTEN STATUS REPORTS WERE SUBMITTED ON THE FOLLOWING DATES.

INSPECTION DATES	PHASE(S) INSPECTED	STATUS REPORT DATES
10/19/99	PROTOCOL APPENDIX/AMENDMENT SUBMISSION	
10/21/99	CLINICAL SIGNS AT 48 HRS.	11/10/99
11/10/99	FINAL REPORT REVIEW	11/10/99

GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

This study was conducted according to:

OECD Principles of Good Laboratory Practice (as revised in 1997) [C(97)186/Final].

Lisa Gayle Bernard

Lisa G. Bernard, M.S.
Study Director

12-1-1999
Month/Day/Year

SIGNATURE PAGE

Lisa G. Bernard, M.S.
Study Director

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Month/Day/Year

John L. O'Donoghue, V.M.D., Ph.D. (pathology)

11/12/99
Month/Day/Year

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ABSTRACT

Crude MCHM

HAEL No.: 97-0216 **EAN: 972790**
PM No.: 18717-00

ACUTE ORAL TOXICITY STUDY IN THE RAT

The purpose of the study was to evaluate the acute toxicity of the test substance in the female Sprague-Dawley rat (Crl:CD(SD)IGS BR) following a single oral dose. Of specific interest, was whether this strain of rat would exhibit hematuria.

A single dose of 500 mg/kg of the neat test substance was administered by gavage to female rats. Abnormal clinical signs were limited to transient reduced activity for all rats and transient stumbling for two rats on the day of dosing. No other abnormal clinical signs were noted at any time during the 14-day observation period. No mortality was observed, and all animals gained weight. No treatment-related changes were observed at necropsy, and no tissues were collected for histological examination.

A single oral dose of 500 mg/kg the test substance did not cause hematuria in female rats of this strain.

STUDY AND TEST SUBSTANCE INFORMATION

Testing Facility

Toxicological Sciences Laboratory
Health and Environment Laboratories
Eastman Kodak Company
Rochester, New York 14652-6272
USA

Project Participants

Study Director:	Lisa G. Bernard, M.S.
Toxicologist:	John W. Mosher, B.S.

Sponsor

Eastman Chemical Company
P.O. Box 431
Kingsport, TN 37662-5280

Sponsor's Representative:
Karen R. Miller, Ph.D.

Test Substance Characterization

Test Substance Name:	Crude MCHM
HAEL No.:	97-0216
EAN No.:	972790
PM No.:	18717-00
SRID No.:	6-97
Physical State and Appearance:	Clear, colorless liquid
Source of Test Substance:	Eastman Chemical Company, Kingsport, TN
Laboratory Project ID:	97-0216A8

Study Dates

Study Initiation Date:	October 19, 1999
Experimental Start Date:	October 19, 1999
Experimental Completion Date:	November 2, 1999

PURPOSE

The purpose of the study was to evaluate the acute toxicity of the test substance in the female Sprague-Dawley rat (Crl:CD(SD)IGS BR) following a single oral dose. Of specific interest, was whether this strain of rat would exhibit hematuria.

MATERIALS AND METHODS

Test System

Five female Sprague-Dawley rats (Crl:CD(SD)IGS BR) obtained from Charles River Laboratories, Stone Ridge (Kingston), NY were randomly assigned to the dose group. The rats were 7 weeks of age and weighed 134 to 158 grams at the start of the study. Rats were chosen for this study because they are a common representative species for toxicity studies. The rat is the preferred rodent species recommended for use in the Organisation for Economic Cooperation and Development (OECD) and European Economic Community (EEC) Test Guidelines.

Husbandry

Housing

Animals were housed in an Association for Assessment and Accreditation of Laboratory Animal Care International-accredited vivarium in accordance with the Guide for the Care and Use of Laboratory Animals (National Research Council, 1996). The rats were singly housed in suspended, stainless-steel, wire mesh cages. Cages and racks were washed once a week. Absorbent paper, used to collect excreta, was changed at least three times a week.

Environmental Conditions

The study room was maintained at 18.5-24.6°C and 38.7-67.2% relative humidity. A photoperiod of 12 hours light from 6 a.m. to 6 p.m. was maintained.

Acclimation Period

The animals were isolated upon arrival and allowed to acclimate for a period of 5 days. Animals were judged to be healthy prior to testing.

Husbandry, continued

Feed

Certified Rodent Diet (PMI #5002, pelleted) was available *ad libitum*. Feed containers were cleaned and refilled at least once a week. No known contaminants which would interfere with the outcome of this study were present in the feed. Analyses of feed are maintained on file within the testing laboratory.

Water

Water was available *ad libitum* through an automatic watering system. The source of the water was the local public water system. There have been no contaminants identified in periodic water analyses that would be expected to interfere with the conduct of the study. Semiannual analyses of water are maintained on file within the testing laboratory.

Identification

Upon arrival, all rats were identified by uniquely-numbered metal ear tags. During randomization, study-specific animal numbers were assigned to each animal. Cage cards contained the study-specific animal number and the ear tag number.

Experimental Design

Test Procedures

This study was conducted according to the Organisation for Economic Cooperation and Development (OECD) Guidelines for Testing of Chemicals: Guideline 401, Acute Oral Toxicity; and European Economic Community (EEC): Annex V., Test B.1, Acute Toxicity (Oral).

Randomization

The procedure for including animals in the study was to randomly select and assign animals from the same shipment to the study. Randomization was done by computer-generated lists. After assignment of animals to the study, the body weights were determined to ensure that individual body weights were within 20% of the mean weight.

Experimental Design, continued

Determination of Dose Levels

A dose of 500 mg of the test substance/kg body weight was selected as the dose level for this study.

Test Substance Exposure

A single dose of the test substance was administered by gavage to animals that had been fasted overnight.

Preparation of Test Substance in the Vehicle

The test substance was administered as received.

Distribution of Animals

TABLE 1

Dose Level	Number Of Animals	Animal Numbers
500 mg/kg	5 Females	551 - 555

Body Weights

Body weights were collected on Days 0 (prior to treatment), 7, and 14.

Clinical Observations

Animals were observed three times on the day of dosing (Day 0), and once each day thereafter for the duration of the experiment. Observations included, but were not limited to, examination of the hair, skin, eyes, mucous membranes, motor activity, feces, urine, respiratory system, circulatory system, autonomic nervous system, central nervous system, and behavior patterns.

Necropsy

All animals were euthanatized and necropsied at the completion of the 14-day observation period.

Data Storage

The final report, data sheets, all nonperishable raw data, and an aliquot of the test substance have been stored in the testing facility archive managed under GLP-mandated conditions.

Data Analysis

No statistical procedures were required during the study. No dose/mortality curve was constructed since graphs become statistically useful only with the use of large numbers of animals and dose groups.

Protocol and Standard Operating Procedure Deviations

There were no SOP or protocol deviations during the study.

RESULTS

Mortality

The dose level, the number of animals administered the test substance at each dose level, the number of deaths, and the Day of death are listed in Table 2.

TABLE 2

Mortality Table

Dose (mg/kg)	Number Of Female Rats Exposed	Number Of Deaths	Time Of Death
500	5	0	- - - - -

Clinical Signs

Abnormal clinical signs were limited to reduced activity and stumbling on the day of dosing. The time of each observation and the number of animals involved at each dose level are listed in Table 3.

TABLE 3

Table Of Clinical Observations

Dose (mg/kg)	Time	Clinical Signs	Number Of Animal Affected
500	Day 0: Immediately and 1 hour after dosing	Appeared Clinically Normal	5/5 Females
500	Day 0: 4 hours after dosing	Reduced Activity Stumbling	5/5 Females 2/5 Females
500	Days 1-14	Appeared Clinically Normal	5/5 Females

Body Weights

All animals gained weight during both weeks of the study. The individual body weights are listed in Table 4.

TABLE 4

Table Of Individual Body Weights (grams)

Dose (mg/kg)	Animal Number	Day 0	Day 7	Day 14
FEMALE RATS				
500	551	134	172	191
500	552	158	199	219
500	553	149	189	211
500	554	144	189	207
500	555	150	178	213

Necropsy Findings

No treatment-related changes were observed at necropsy, and no tissue was collected for microscopic examination. A record of the incidence and severity of all gross abnormalities is presented in computer-generated tables which are included in the Appendix.

DISCUSSION

For the female Sprague-Dawley rats (Crl:CD(SD)IGS BR) used in this study, abnormal clinical signs were limited to transient reduced activity and stumbling on the day of dosing.. No red urine or hematuria were observed following treatment in this study.

In a previous study conducted using a different strain of Sprague-Dawley rat [SAS:VAF(SD)], female rats administered a comparable dose of the test substance exhibited similar signs of transient slight weakness and stumbling on the day of dosing. However, these animals also exhibited red urine and/or hematuria (TX-97-306, 1998).

CONCLUSION

A single oral dose of 500 mg/kg the test substance did not cause hematuria in female rats of this strain.

REFERENCES

National Research Council (1996). *Guide for the Care and Use of Laboratory Animals.* National Academy Press. Washington, D.C.

TX-97-306 (1998). Crude MCHM: Acute Oral Toxicity Study In The Rat. Unpublished report, Health and Environment Laboratories, Eastman Kodak Company.

APPENDIX

SUMMARY GROSS PATHOLOGY INCIDENCE TABLE - FEMALE RATS

GROUP	500 MG/KG
TRACHEA	5
LUNGS	5
THYMUS	5
HEART	5
ESOPHAGUS	5
STOMACH	5
DUODENUM	5
JEJUNUM	5
ILEUM	5
CECUM	5
COLON	5
RECTUM	5
LIVER	5
KIDNEYS	5
URINARY BLADDER	5
PITUITARY GLAND	5
ADRENALS	5
PANCREAS, NOS	5
THYROID GLANDS	5
PARATHYROID GLANDS	5
SPLEEN	5
MESENTERIC LYMPH NODES	5
BONE MARROW	5
BRAIN	5
EYES	5
SALIVARY GLANDS	5
ADIPOSE TISSUE	5
SKIN, NOS	5
HAIR	5
FALLOPIAN TUBES	5
VAGINA	5
UTERUS	5
HYDROMETRA	1
OVARIES	5
CERVIX UTERI	5

NUMBERS REPRESENT NUMBER OF TISSUES EXAMINED, OR IN THE CASE OF ABNORMAL FINDINGS, THE NUMBER OF TISSUES WITH EACH ABNORMALITY

INDIVIDUAL ANIMAL GROSS PATHOLOGY INCIDENCE TABLE - FEMALE RATS

500 MG/KG

ANIMAL # / DAYS ON TEST	551 / 14	552 / 14	553 / 14	554 / 14	555 / 14
TRACHEA	X	X	X	X	X
LUNGS	X	X	X	X	X
THYMUS	X	X	X	X	X
HEART	X	X	X	X	X
ESOPHAGUS	X	X	X	X	X
STOMACH	X	X	X	X	X
DUODENUM	X	X	X	X	X
JEJUNUM	X	X	X	X	X
ILEUM	X	X	X	X	X
CECUM	X	X	X	X	X
COLON	X	X	X	X	X
RECTUM	X	X	X	X	X
LIVER	X	X	X	X	X
KIDNEYS	X	X	X	X	X
URINARY BLADDER	X	X	X	X	X
PITUITARY GLAND	X	X	X	X	X
ADRENALS	X	X	X	X	X
PANCREAS, NOS	X	X	X	X	X
THYROID GLANDS	X	X	X	X	X
PARATHYROID GLANDS	X	X	X	X	X
SPLEEN	X	X	X	X	X
MESENTERIC LYMPH NODES	X	X	X	X	X
BONE MARROW	X	X	X	X	X
BRAIN	X	X	X	X	X
EYES	X	X	X	X	X
SALIVARY GLANDS	X	X	X	X	X
ADIPOSE TISSUE	X	X	X	X	X
SKIN, NOS	X	X	X	X	X
HAIR	X	X	X	X	X
FALLOPIAN TUBES	X	X	X	X	X
VAGINA	X	X	X	X	X
UTERUS	X	X	X	X	
HYDROMETRA					2
OVARIES	X	X	X	X	X
CERVIX UTERI	X	X	X	X	X

KEY: N-NORMAL AND TISSUE COLLECTED FOR HISTOPATHOLOGY, X-NORMAL BUT NOT COLLECTED, 1-MINIMAL, 2-MINOR, 3-MODERATE, 4-SEVERE, P-PRESENT, A-ABSENT, * -SEE COMMENT REPORT